

**Remarks**

Claims 1-19 are pending. Claim 20 has been cancelled. Claim 19 has been amended to distinguish the claim from claim 14 and address the objection to claim 19 under 37 CFR 1.75(c). The amendment to the claim is supported at, for example, paragraph [0072]. No new matter is added.

Claims 1-5, 7 and 9-13 stand rejected under 35 U.S.C. § 102 as being anticipated by Itoi, U.S. Patent No. 6,159,437.

Claim 6 stands rejected under 103(a) as being unpatentable over Itoi, U.S. Patent No. 6,159,437, alone and in view of Kumta et al., U.S. Patent No. 7,247,288.

Claims 14-19 stand rejected under 103(a) as being unpatentable over Kumta et al., U.S. Patent No. 7,247,288, in view of Fujishiro, et al., "Coating of Hydroxyapatite on Titanium Plates Using Thermal Dissociation of Calcium-EDTA Chelate Complex in Phosphate Solutions Under Hydrtothermal Conditions", Journal of Colloid and Interface Science 173, 119-127 (1995).

The applicant respectfully maintains that the Examiner has failed to establish a *prima facie* case of obviousness in this case. The references cited by the Examiner, when read in their entirety from the perspective of one skilled in the art, do not describe, teach or suggest all of the limitations recited in claims 1-19 as amended.

**Scope and Content of the Cited Art**

Itoi, U.S. Patent No. 6,159,437 describes an apatite slurry comprised of apatite particles which are dispersed in a water compatible organic solvent and which has a degree of dispersion such that the average particle size of the apatite particles is 1  $\mu\text{m}$  or less and particles of 3  $\mu\text{m}$  or less are "practically absent". Col. 1, lines 7-14. Itoi describes a slurry of apatite particles which

are aggregates of apatite crystal particles. Itoi states that “[g]enerally, apatite particles are formed by aggregation of such primary particles to a size of about 10  $\mu\text{m}$  to 100  $\mu\text{m}$ .” Col. 3, lines 33-35.

The primary particles described in Itoi are “apatite crystal particles with a short axis length of 10 to 100 nm and a long axis length of 30 to 300 nm.” Col. 3, lines 26-27. According to Itoi, these apatite crystal particles form larger particles of 10  $\mu\text{m}$  to 100  $\mu\text{m}$  in diameter. It is these larger particles that are dispersed in a water soluble organic solvent to form the apatite slurry described by Itoi. The larger particles are suspended and dispersed in the water-compatible organic solvent and the resulting slurry is dispersed using an agitation mill to achieve the final dispersion. Col. 4, lines 33-59. A dispersion agent, such as sodium hexametaphosphate or sodium tripolyphosphate, may be added to the slurry. Col. 3, lines 53-57. As shown in Table 1 and the figures of Itoi, all of the slurries described in Itoi include substantial amounts of particle apatite having particle size larger than 500 nm.

Kumta, U.S. Patent No. 7,247,288, describes a method for producing nanocrystalline hydroxyapatite particles having a diameter in the range of about 1 nm to about 100 nm. Col. 8, lines 19-22. The hydroxyapatite particles are produced by combining calcium and a non-ionic phosphate, such as trisodium phosphate, in the presence of hydroxyl ions, such as from sodium hydroxide. Col. 8, lines 1-4, Example 1. The reaction is carried out with calcium ions far outnumbering phosphate ions in the reaction solution. Col. 4, lines 47-54; col 8, lines 6-9. According to Kumta, the initial pH of the solution is about 12, and decreases only slightly after the reactants are combined. Col. 15, lines 47-67 and Fig. 1.

Kumta also describes incorporating the hydroxyapatite particles produced from the process into a substrate or depositing the hydroxyapatite particles on a substrate. Col. 8, lines 44-49. The substrate may be a “matrix, such as a biomimetic extracellular matrix, which is a synthetic matrix that is intended to mimic a natural extracellular matrix in its structure and/or function.” Col. 8, lines 49-53. Kumta states that the matrix may be a natural or synthetic polymer. Col. 8, lines 53-55.

The hydroxyapatite described by Kumta is not present in a colloidal dispersion. In describing the incorporation of the hydroxyapatite with the extracellular matrix, Kumta states that the hydroxyapatite is associated with or incorporated in the matrix by adding the hydroxyapatite to the matrix polymer during polymerization or cross-linking. Col. 8, line 44 to col. 9, line 2. The resulting material is illustrated in Fig. 11 of Kumta, which clearly shows hydroxyapatite particles that are embedded within the polymer matrix.

Fujishiro describes coating titanium plates with hydroxyapatite using a homogeneous precipitation technique. The process described by Fujishiro involved the use of hydrothermal reactions of  $\text{Ca}(\text{edta})^2$  -  $\text{NaH}_2\text{PO}_4$  solution at 120-200°C and pH 4.0-10.0 for 2-20 hours. Fujishiro describes coating the titanium plates with hydroxyapatite using the  $\text{Ca}(\text{edta})^2$  -  $\text{NaH}_2\text{PO}_4$  solution at pH 6-9 at a temperature of 160°C. As reported by Fujishiro, the resulting hydroxyapatite “consisted of needle-like particles and/or rod-like particles, 50  $\mu\text{m}$  in length and 3  $\mu\text{m}$  in diameter.” Pages 123-124.

**Differences Between Prior Art and Claims At Issue****Rejection of Claims 1-5, 7 and 9-13 Under 35 U.S.C. § 102 Based on Itoi**

Claim 1 recites a colloidal dispersion of calcium phosphate platelets wherein the length of the platelets, L, is between 5 nm and 500 nm and the thickness of the platelets is between 0.5 and 20 nm, and at least one polymer that complexes calcium. As set forth in the application in Paragraph 0024, “platelets” refers to bar or strip shapes and more generally any volume which has a low thickness and a greater length than width.” Claims 2-5, 7 and 9-13 depend directly or indirectly from claim 1 and recite additional features of the claimed colloidal hydroxyapatite dispersion.

To anticipate a claim under 35 U.S.C. § 102, each and every element as set forth in the claim must be found in a single prior art reference. MPEP § 2131. Itoi does not anticipate claims 1-5, 7 and 9-13 for at least two reasons: (1) Itoi does not describe a dispersion having particle sizes within the claimed range, and (2) Itoi does not describe a dispersion including at least one polymer that complexes calcium.

In the Office Action at page 2, the Examiner states that Itoi describes a dispersion of apatite particles having a size of 10-100 nm in the short-axis and 30-300 nm in the long axis. This reading of Itoi is mistaken. The particle size referred to by the examiner is the particle size of the *primary particles* of apatite. Itoi describes using apatite particles formed from the primary particles to produce the slurry. The particles used to form the slurry have particle sizes of 10  $\mu\text{m}$  to 100  $\mu\text{m}$ . Col. 3, lines 33-35. These larger particles are dispersed in an organic solvent and water, and agitation milled to produce a slurry. As shown in Table 1 and the Figures in Itoi, the resulting slurry has a substantial number of particles (at least about 15% or more) with a size

above the 500 nm particle size recited in claim 1. Accordingly, the slurry described in Itoi does not anticipate the colloidal dispersion recited in claim 1 for at least this reason.

In addition, the slurry described by Itoi does not include a polymer that complexes with calcium. The Examiner points to the dispersion agents described by Itoi as meeting the complexing polymer limitation of claim 1. A dispersion agent is not a complexing polymer as described in the present application. Indeed, at Paragraph [0037], the application describes the use of dispersing agents, including the sodium tripolyphosphate described by Itoh, in the colloidal dispersion in addition to the complexing polymer. Accordingly, Itoi does not describe a slurry having a polymer that complexes calcium as described in the application and recited in claim 1, and claim 1 is not anticipated by Itoi for at least this additional reason.

Because claim 1 is not anticipated by Itoi, dependent claims 2-5, 7 and 9-13 are not anticipated by Itoi for at least the same reasons.

#### Rejection of Claim 6 Under 35 U.S.C. § 103 Based Upon Itoi and Kumta

Although it is not explicitly stated in the office Action, it appears that at pages 3 and 4 of the Office Action, the Examiner rejects claim 6 as obvious in view of Itoh alone, as well as based upon Itoh in view of Kumta. These references do not establish a *prima facie* case of obviousness of claim 6.

Regarding the rejection of claim 6 based upon Itoh in view Kumta, as set forth above, Itoh does not describe or suggest a colloidal dispersion having a particle size within the range set forth in claim 1, nor does Itoh describe a slurry containing a polymer that complexes calcium as recited in claims 1. The Examiner does not cite Kumta to address the first deficiency of Itoh

related to particle size, and therefore the combination of Itoh and Kumta does not result in a colloidal dispersion meeting all of the limitations of claim 1. Accordingly, the Examiner's obviousness rejection is improper for at least this reason.

The Examiner does cite Kumta as describing the use of a polymer that complexes calcium. In this case, however, Kumta does not teach the use of a polymer to complex the apatite to form a colloidal dispersion. Rather, Kumta describes certain polymers that may be used to form a biomimetic extracellular matrix. Kumta further describes incorporating hydroxyapatite in the extracellular matrix by adding hydroxyapatite to the polymer used to form the extracellular matrix during polymerization or cross-linking. As illustrated in Fig. 11 of Kumta, the resulting material comprises hydroxyapatite particles within the polymer matrix, and it does not describe a colloidal dispersion at all, much less a dispersion of the type recited in claim 6. Indeed, while Kumta describes incorporating formed apatite particles in the extracellular matrix, in the colloidal dispersion of the present application, the polymer that complexes calcium is added to the solution used to form the hydroxyapatite before the heat treatment stage in which the hydroxyapatite is formed. Kumta does not teach or suggest use of a polymer that complexes calcium in a colloidal dispersion of the type recited in claim 6, and claim 6 is not obvious in view of the combination of Itoh and Kumta for at least this additional reason.

Rejection of Claims 14-19 Under 35 U.S.C. § 103 Based Upon Kumta in View of Fujishiro

Claim 14 describes a process for producing a dispersion of calcium phosphate platelets and at least one polymer which complexes calcium. The process of claim 14 requires that the pH of the solution in which the calcium phosphate platelets is formed must be adjusted to a selected

value between 4 and 6 and maintained at the selected value between 4 and 6 while the calcium phosphate platelet dispersion is formed. The process of claim 14 also requires that a polymer that complexes calcium be added to the reaction solution prior to heating the solution to the required temperature for hydroxyapatite formation. Claims 15-19 depend from claim 14

Kumta, U.S. Patent No. 7,247,288, describes a method for producing nanocrystalline hydroxyapatite particles having a diameter in the range of about 1 nm to about 100 nm. Col. 8, lines 19-22. The hydroxyapatite particles are produced by combining calcium and a non-ionic phosphate, such as trisodium phosphate, in the presence of hydroxyl ions, such as from sodium hydroxide. Col. 8, lines 1-4, Example 1. The reaction is carried out with calcium ions far outnumbering phosphate ions in the reaction solution. Col. 4, lines 47-54; col 8, lines 6-9. According to Kumta, the initial pH of the solution is about 12, and decreases only slightly after the reactants are combined. Col. 15, lines 47-67 and Fig. 1.

Kumta does not describe a process for producing a colloidal suspension including a polymer that complexes with calcium as recited in claim 14. The Examiner cites a portion of Kumta, col. 22, lines 23-29, as disclosing the use of a polymer in the process described in Kumta, and suggests that this meets the limitation of claim 14 reciting the addition of a polymer that complexes calcium. In the portion cited by the Examiner, Kumta describes forming a membrane which includes hydroxyapatite, i.e., the formed hydroxyapatite is contained within the polymeric structure of the membrane as stated at column 22, lines 28-30. Accordingly, Kumta describes a solid polymer matrix containing hydroxyapatite particles, and Kumta does not describe a colloidal dispersion at all, much less the colloidal dispersion formed by the method of claims 14-19.

The deficiencies in Kumta described above are not addressed in any way by Fujishiro, and claims 14-19 are therefore patentable over Kumta and Fujishiro for at least the reasons stated above. In addition, one skilled in the art would not be motivated to combine Kumta and Fujishiro in the manner suggested by the Examiner to arrive at the method of claims 14-19. The Examiner recognizes that Kumta does not describe or suggest forming hydroxyapatite at a pH between 4 and 6. The Examiner cites Fujishiro as describing a process that uses a solution with a pH between 4 and 6 to produce hydroxyapatite, and suggests that one skilled in the art would be motivated to modify the process of Kumta by adjusting the pH to between 4 and 6 based on Fujishiro. The Examiner fails to consider that Fujishiro teaches that the process described results in hydroxyapatite particles having a size of 50  $\mu\text{m}$  in length and 3  $\mu\text{m}$  in diameter, orders of magnitude larger than the particles produced by the method recited in claims 14-19. Accordingly, one skilled in the art seeking to produce a colloidal dispersion comprising particles that are no more than 500 nm in length would not combine the process of Kumta with the pH described by Fujishiro to arrive at the claimed method. When Kumta and Fujishiro are read as a whole, they do not describe or suggest the process recited in claims 14-19, and the rejection of these claims based on Kumta and Fujishiro should be withdrawn.

In view of the amendments to the claims and the foregoing remarks, the pending claims are believed to be allowable over the prior art of record. Accordingly, it is respectfully requested that this application be allowed and a Notice of Allowance issued. If the Examiner believes that a telephone conference with Applicants' attorney would be advantageous to the disposition of this case, and in particular if a terminal disclaimer is required for allowance, the Examiner is cordially requested to telephone the undersigned. If the Examiner has any questions in

connection with this paper, or otherwise if it would facilitate the examination of this application, please call the undersigned at the telephone number below.

Because the reasons above are sufficient to traverse the rejection, Applicants have not explored, nor do they now present, other possible reasons for traversing such rejections. Nonetheless, Applicants expressly reserve the right to do so, if appropriate, in response to any future Office Action.

A Petition for a One Month Extension of Time along with the associated fees are filed herewith. No additional fee is believed to be required. In the event the Commissioner of Patents and Trademarks deems additional fees to be due in connection with this application, Applicant's attorney hereby authorizes that such fee be charged to Deposit Account No. 50-3569.

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Respectfully submitted,

  
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